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#10

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/719,742	09/25/96	WILLIAMS	L 1172.003

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EXAMINER

LAZAR WESLEY, E

ART UNIT

PAPER NUMBER

1646

DATE MAILED:

06/11/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/719,742

Applicant(s)

Williams

Examiner

Eliane Lazar-Wesley

Group Art Unit

1646



☒ Responsive to communication(s) filed on February 26 and March 31, 1999.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-5 and 7-53 is/are pending in the application.

Of the above, claim(s) 16-22, 24, and 45-48 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-5, 7-15, 23, 25-44, and 49-53 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

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DETAILED ACTION

1. The amendment filed February 26, 1999, and March 31, 1999 have been entered.

Claims 1-5, 7-15, 23, 25-44 and 49-53 are under consideration. Claims 1, 4, 13, 23 and 25-27 have been amended.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

3. Claims 13-15, and 43-44 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record, because the specification, while being enabling for repairing epithelial cell damage, does not reasonably provide enablement for preventing epithelial cell damage. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Applicants arguments have been considered but are not found persuasive.

ew Applicants argue, page 5, last paragraph, that a sufficient disclosure has been provided regarding how to make the compositions. Applicant's attention is brought to the fact that the Examiner did not reject claims to compositions, but rejected claims to methods of repairing and preventing, and that the argument is about methods of preventing. Applicants argue, page 6, last paragraph, that the methods are not limited to preventing burns, but that, for example, the method could be used to prevent ulcers. While it is reasonable that the claimed pharmaceutical composition and method would be enabled for treatment of epithelial cell damage, prevention is an absolute term,

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and absolute prevention has not been demonstrated, nor has guidance been provided as for absolute prevention , like doses, methods of administration, etc... What is questioned here is not safety or efficacy, as argued by applicants on page 7, first paragraph, but a degree of effect, which is appropriate under a rejection under 35 USC § 112, first paragraph. It seems unpredictable if not impossible to prevent epithelial cell damage like the one occurring during a severe mechanical or burn injury. While the examiner used burns only for the purpose of an example in the rejection, and while the examiner agrees with applicant's argument that it is desirable to prevent ulcers , the specification does not provide guidance as of , for example, how to administer the protein to the gastric or intestinal lining without the protein being degraded, and the specification does not teach that prevention could be achieved.

4. Claims 1-5, 7-15, 23, 25-44 and 49-53 are or remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 13 are indefinite, because they do not provide the metes and bounds of what a biologically active fragment or biologically active analog or biologically active derivative of "a PDGF" or "a KGF" are. There is no reference sequence given for the PDGF or KGF, and it is not clear what the deletion and substitution are compared to. Furthermore, it is not clear what is encompassed by a biologically active analog or a biologically active derivative of PDGF or KGF, and there is no structural features provided for such analog. The biologically active analog is recited as comprising at least one amino acid substitution, deletion, or addition. However, there is no limit as of how many

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substitutions, deletions or additions are envisioned, and the resulting analog might be structurally unrelated to PDGF and KGF. The specification, page 10, line 14-15, recites that analogs include peptide mimics, or peptoids, that possess the bioactivity of the protein. As stated in the former office action, page 3, paragraph 6, other growth factors or molecules have the same biological activities of stimulating the growth of cells in the dermis, and mimics that possess the bioactivity of the protein are likely to encompass molecules that have very little, if any, structural relationship with the reference molecule. Applicants argument, page 8, first paragraph, that the amendments overcome the rejection, is not persuasive, because there is no upper limit as of how many substitutions, deletions or additions are envisioned, and therefore as what the structure of the biologically active analog is.

As the metes and bounds of "a biologically active analog of KGF comprising at least one amino acid substitution, deletion or addition, and a biologically active derivative of a KGF" are not defined clearly, the claims read on wild type KGF, on recombinant KGF and on truncated KGF.

Claims 25 and 27 have the additional limitation of comprising a third (IGF) and a fourth (IGFBP) polypeptide. These claims recite also a biologically active fragment of IGF or IGFBP, a biologically active analog and a biologically active derivative of IGF or IGFBP. The claims are indefinite for the same reasons as discussed for claims 1 and 13.

Claim Rejections - 35 USC § 102

5. Claims 1-5, 7-15 and 23 are or remain rejected under 35 U.S.C. 102(a) as being anticipated by Ring et al., Growth factors in Porcine full and partial thickness burn repair, Wound repair and

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regeneration, Fifth annual meeting of the wound healing society, Minneapolis, MN April 27-30, 1995, issue of January-March 1995.

Ring et al. teach a combination of rPDGF and rKGF that results in a significant increase in new epithelial area in the treatment of burns. As the metes and bounds of "a biologically active analog of KGF comprising at least one amino acid substitution, deletion or addition, and a biologically active derivative of a KGF" are not defined clearly, as discussed in the rejection under 35 USC § 112, second paragraph, above, the claims read on wild type KGF, on recombinant KGF and on truncated KGF, and the limitations of the claims are met.

While applicants argues that Ring "appears to use full-length recombinant KGF", Applicant's arguments are not found persuasive, for the reasons discussed. Specifically, as no specific sequence is recited (as discussed in the rejection under 35 USC § 112, second paragraph, supra), the protein used by Ring meets the limitations of the claims

Claim Rejections - 35 USC § 103

6. Claims 25-44 and 52-53 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ring et al., Growth factors in Porcine full and partial thickness burn repair, Wound repair and regeneration, Fifth annual meeting of the wound healing society, Minneapolis, MN April 27-30, 1995, issue of January-March 1995, cited by applicants, in view of Martin et al., Progress in growth factor research 4:25-44, 1992, Antoniades et al., US Patent 4,861,757, Gospodarowicz et al., US Patent

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5,677,278, Jyung et al., Surgery 115(2):233-9, February 1994 (W) and Yanni, US Patent No 5,624,893 (A) for the reasons of record in the former office action

Applicant's arguments have been fully considered but have not been found persuasive. Applicant did not respond to the rejection as he did not consider the combination of references. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

While applicants argues that Ring "appears to use full-length recombinant KGF", Applicant's arguments are not found persuasive, for the reasons discussed. Specifically, as no specific sequence is recited (as discussed in the rejection under 35 USC § 112, second paragraph, supra), the protein used by Ring meets the limitations of the claims

Furthermore, contrary to applicants arguments that there is no suggestion of using biologically active fragment of KGF, Gospodarowicz teaches a biologically active fragment of KGF that is more potent than full-length KGF and is useful for wound healing.

Applicant's argument that the composition of Yanni contains bradykinin antagonists or neurokinin antagonists is not relevant, because these components are present for the purpose of analgesic or pain modulating properties (col.3, lines 28-31) and not for wound healing. Applicants' arguments that Yanni provides only a laundry list of compounds and not the specific

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combinations is not persuasive, because applicants specific combination of growth factors for wound healing does not show unexpected properties relative to each of its element.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the combination of PDGF and KGF taught by Ring, the synergistic action of PDGF with other growth factors in wound healing taught by Martin, the combination of PDGF and IGF-I taught by Antoniades, and the combination of IGF-I and IGFBP-I taught by Jyung, and the combination of wound healing modulators taught by Yanni, have been taught as potent in wound healing, as discussed in the former Office action on page 5 and 6. Such teachings would certainly motivate one of skill in the art to combine PDGF, KGF, IGF and IGFBP in a composition, and give him reasonable expectation of success in making a composition and a method for treatment of epithelial cell damage that are at least as potent as the compositions and methods taught in the prior art.

In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

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7. Claims 49-51 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ring et al., Growth factors in Porcine full and partial thickness burn repair, Wound repair and regeneration, Fifth annual meeting of the wound healing society, Minneapolis, MN April 27-30, 1995, issue of January-March 1995, cited by applicants, in view of Martin et al., Progress in growth factor research 4:25-44, 1992, Antoniadis et al., US Patent 4,861,757, Gospodarowicz et al., US Patent 5,677,278, Jyung et al., Surgery 115(2):233-9, February 1994 (W). and Yanni, US Patent No 5,624,893 (A) , as recited for claims above, and further in view of Song et al., US Patent 5,399, 361 for the reasons of record.

Applicants arguments have not been found persuasive for the reasons discussed above. The Song reference had been added in the rejection to show that it was well known to deliver pharmaceutical compositions for wound healing by means of a sponge, for example, as discussed in the former Office action, page 7.

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eliane Lazar-Wesley, PhD, whose telephone number is (703) 305 4059. The examiner can normally be reached on Monday-Friday from 8:30am to 5pm.

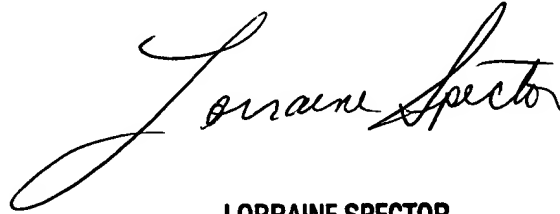
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308 4310.

Official papers filed by fax should be directed to (703) 308 4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

ELW
May 24, 1999

EW

A handwritten signature in cursive script that reads "Lorraine Spector". The signature is written in black ink and is positioned above the printed name.

**LORRAINE SPECTOR
PRIMARY EXAMINER**